肠道菌群作为中药治疗心血管疾病的靶标: 潜在的机制和治疗策略

乐琬琪[1], 廖景瑜[1], 张榆浩[1,2], 吴高松[1*], 张卫东[1,2,3*]

(1. 上海中医药大学交叉科学研究院, 上海 201203; 2. 中国药科大学中药学院, 江苏 南京 211198;
3. 中国人民解放军海军军医大学药学院, 上海 200433)

摘要: 心血管疾病 (cardiovascular disease, CVD) 是全球范围内造成患者死亡的主要因素, 其发病机制复杂且死亡率逐年增高。大量研究显示, 肠道菌群及其代谢产物与心血管疾病的发生发展密切相关, 肠道菌群有望成为治疗心血管疾病潜在的新靶点。中药具有多组分、多靶点和整体性的特点, 可通过调控肠道菌群发挥对心血管疾病的治疗作用, 在稳定病情、改善心脏功能、提高生活质量等方面具有明显的优势, 是一种理想的肠道微生态调节剂。因此, 本综述将主要讨论肠道菌群及其代谢产物与心血管疾病的密切关联, 中药靶向肠道菌群改善心血管疾病的治疗策略, 包括调节肠道菌群组成、保护肠道黏膜屏障、影响肠道免疫功能和调控肠道菌群代谢产物, 为中药靶向肠道菌群治疗心血管疾病的研究提供参考。

关键词: 肠道菌群; 肠道菌群代谢产物; 心血管疾病; 中药; 作用机制

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Gut microbiota as a target for traditional Chinese medicine in the treatment of cardiovascular disease: potential mechanisms and therapy strategies

LE Wan-qi[1], LIAO Jing-yu[1], ZHANG Yu-hao[1,2], WU Gao-song[1*], ZHANG Wei-dong[1,2,3*]

(*1. Institute of Interdisciplinary Integrative Medicine Research, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China; 2. School of Traditional Chinese Pharmacy, China Pharmaceutical University, Nanjing 211198, China; 3. School of Pharmacy, Second Military Medical University, Shanghai 200433, China*)

Abstract: Cardiovascular disease (CVD) is a major contributor to patient deaths worldwide, and its pathogenesis is complex and mortality rates are increasing every year. Numerous researches have shown that the gut microbiota and its metabolites were closely associated with the development of CVD, and gut microbiota was expected to be a potential new target for the treatment of CVD. Traditional Chinese medicine (TCM), characterized by its multi-component, multi-target and integrity, can play a therapeutic role in CVD by regulating the gut microbiota, which has obvious advantages in stabilizing the disease, improving heart function and enhancing quality of life, and is an ideal intestinal microecological regulator. Therefore, this review will mainly discuss the intimate association of gut microbiota and its metabolites with CVD, and the therapeutic strategies of TCM targeting gut microbiota to improve CVD, including regulating the composition of gut microbiota, protecting the intestinal mucosal barrier, influencing the intestinal immune function and modulating the metabolites of gut microbiota, in order to provide a reference for the research of TCM targeting gut microbiota for CVD.

Key words: gut microbiota; metabolite of gut microbiota; cardiovascular disease; traditional Chinese medicine; mechanism of action

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*通讯作者 Tel / Fax: 86-21-81871244, E-mail: wdzhangy@hotmail.com; gaosong1276@163.com

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当前我国人口老龄化加剧, 心血管疾病 (cardiovascular disease, CVD) 负担日益加重, CVD 死亡占城乡居民总死亡原因的首位[1]。目前, CVD 的临床常用药物包括血管紧张素转换酶抑制剂、血管紧张素受体拮抗剂、他汀类药物、β受体阻断剂、钙离子拮抗剂和利尿剂等, 都存在不同程度的不良反应[2]。肠道菌群具有调节免疫、保护肠道屏障完整性、维持代谢稳态等功能, 与CVD之间存在密切联系[3]。研究显示, 中药可以靶向肠道菌群, 促进CVD患者肠道有益菌的生长并抑制致病菌的繁殖发挥治疗作用, 并显示出很好的效果[4]。靶向肠道菌群, 揭示中药治疗CVD的作用机制, 或许能研究出更加有益的CVD治疗药物。本研究将对近5年关于CVD的肠道菌群研究和中药靶向肠道菌群治疗CVD的文献进行系统总结, 并从以下3个方面进行系统综述: ① 肠道菌群菌落组成与CVD的关联; ②肠道菌群代谢产物与CVD的关联; ③中药靶向肠道菌群治疗CVD的策略 (图1)。

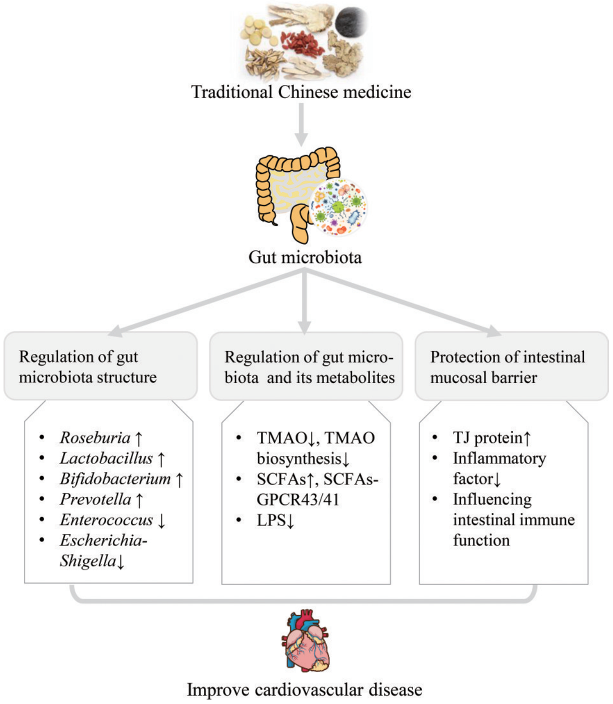

Figure 1 Mechanism of action of traditional Chinese medicine targets gut microbiota for cardiovascular diseases. TMAO: Trimethylamine-*N*-oxide; SCFAs: Short chain fatty acids; GPCR: G protein coupled receptors; LPS: Lipopolysaccharide; TJ: Tight junction

1 肠道菌群菌落组成与心血管疾病的关联

CVD 包括动脉粥样硬化 (atherosclerosis, AS)、急性心肌梗死 (acute myocardial infarction, AMI)、心力衰竭 (heart failure, HF)、高血压和心律失常等, 其发病率和死亡率逐年增加, 在全球范围内造成了巨大的经济和健康负担[5]。肠道菌群通过免疫调节在CVD病理进展中起着关键作用, 心肌损伤会诱导肠道菌群失调和肠道屏障破坏, 从而导致细菌易位, 这些变化反过来通过改变心肌免疫激活和炎症反应加重心肌损伤[6]。一般情况下, 健康机体肠道菌群的组成相对稳定, 主要由厚壁菌门Firmicutes、拟杆菌门Bacteroidetes、变形菌门Proteobacteria和放线菌门Actinobacteria组成; 肠道菌群组成的稳定对于维持肠道微生态平衡至关重要, 一旦这种平衡被破坏, 不仅会增加肠道疾病的发病风险, 还会引起CVD的发生[7]。表1[8-18]总结了近年来在不同类型CVD患者肠道菌群组成和相对丰度变化的研究。

1.1 AS AS是一种慢性炎症性疾病, 其特征是脂肪和纤维物质在动脉内膜层堆积导致血管壁逐渐增厚变硬[19]。在AS患者中, 克雷伯氏菌属*Klebsiella*细菌的相对丰度显著升高, 乳酸杆菌属*Lactobacillus*、罗斯氏菌属*Roseburia*、普雷沃氏菌属*Prevotella*和双歧杆菌属*Bifidobacterium*细菌的相对丰度显著降低, 在高血压、慢性心力衰竭 (chronic heart failure, CHF) 和冠心病患者中同样存在上述变化[8,9,13,15,17]。克雷伯氏菌属细菌是引起肺炎、脑膜炎、呼吸道感染、尿路感染、腹膜炎、腹泻和败血症的条件致病菌[20]。乳酸杆菌属细菌是能产生短链脂肪酸 (short chain fatty acids, SCFAs) 的有益菌, 它可调节与CVD风险相关的肠道菌群及其代谢产物, 并通过抑制病原体来降低肠道通透性, 减少炎症和氧化应激, 从而预防和治疗CVD[21]。罗斯氏菌属细菌也是SCFAs (特别是丁酸) 产生菌, 具有影响结肠动力、免疫维持和抗炎特性, 能保护肠道免受病原体的侵害[22]。普雷沃氏菌属细菌可利用多糖产生SCFAs从而预防CVD[23]。双歧杆菌属细菌可通过产生SCFAs和调节相关趋化因子来减轻炎症反应[24]。

1.2 AMI AMI是由于冠状动脉急性闭塞和血流中断, 导致心肌细胞持续缺血缺氧引起的心肌坏死[25]。在AMI患者中巨球形菌属*Megasphaera*和脱硫弧菌属*Desulfovibrio*细菌的相对丰度显著升高, 毛螺菌科*Lachnospiraceae*、真杆菌属*Eubacterium*细菌的相对丰度显著降低, 在AS、CHF、高血压和冠心病患者中同样存在上述变化[10,11,13-16]。巨球形菌属细菌可产生SCFAs、维生素和必需氨基酸等重要代谢产物, 对宿主健康产生有益影响[26]。脱硫弧菌属细菌分泌的外膜囊泡能抑制紧密连接蛋白 (tight junction proteins) 的表达, 破坏肠上皮屏障, 诱导炎症因子产生并导致巨噬细胞炎症和焦亡[27]。毛螺菌科细菌丰度在含不饱和脂肪酸的饮食干预后增加, 与CVD危险因素呈负相关[28]。

Table 1　Changes in the composition and abundance of gut microbiota in different types of cardiovascular diseases

Cardiovascular disease	Research subject	Change in the relative abundance of gut microbiota		Ref.
		Increase	Reduction	
Atherosclerosis	218 individuals with atherosclerotic cardiovascular disease	*Escherichia coli*, *Klebsiella* spp., *Enterobacter aerogenes*, *Ruminococcus gnavus*, *Eggerthella lenta*, *Streptococcus* spp., *Lactobacillus sativarius*, *Solobacterium moorei*, *Atopobium parvulum*	*Bacteroides* spp., *Prevotella copri*, *Alistipes shahii*, *Roseburia intestinalis*, *Faecalibacterium cf. prausnitzii*	[8]
	Male C57/BL6 apolipoprotein E-deficient mice	*Faecalibaculum*, *Oscillibacter*, *Eubacterium_coprostanoligenes_group*, *Blautia*	*Muribaculaceae*, *Lactobacillus*, *Ileibacterium*, *Bifidobacterium*	[9]
	Male New Zealand white rabbits	*Akkermansia*, *Islandicum*, *Desulfovibrio*	*Succinispira mobilis*, *Alipipes*, *Indistinctus*, *Campylobacter*, *Odoribacter*, *Subantarcticus*	[10]
Acute myocardial infarction	30 acute myocardial infarction patients	*Megasphaera*, *Butyricimonas*, *Acidaminococcus*, *Desulfovibrio*	*Tyzzerella 3*, *Dialister*, [*Eubacterium*] *ventriosum group*, *Pseudobutyrivibrio*, *Lachnospiraceae ND3007 group*	[11]
Heart failure	53 chronic heart failure patients	*Ruminococcus*, *Acinetobacter*, *Veillonella*	*Alistipes*, *Faecalibacterium*, *Oscillibacter*	[12]
	Male BALB/C mice	*Bilophila*, *Enterococcus*, *Erysipelatoclostridium*, *Escherichia-Shigella*	*Roseburia*, *Lactobacillus*, *Lachnospiraceae_UCG-006*, *Prevotellaceae_UCG-001*, *Ruminococcaceae_UCG-014*, *Erysipelotrichaceae*, *Mollicutes_RF39*, *Candidatus_Saccharimonas*	[13]
	29 chronic heart failure patients	*Enterococcaceae*, *Enterococcus*	*Ruminococcaceae UCG-004*, *Ruminococcaceae UCG-002*, *Lachnospiraceae FCS020 group*, *Dialister*	[14]
Hypertension	2 372 hypertension patients	*Megasphaera*, *Escherichia_Shigella*, *Klebsiella*	*Bifidobacterium*, *Faecalibacterium*, *Roseburia*, *Ruminococcus*	[15]
Coronary heart disease	42 stable coronary artery disease patients	*Ralstonia*, *Enterococcus*, *Megasphaera*	*Paraprevotella*, *Barnesiella*, *Phascolarctobacterium*, *Faecalibacterium*, *Clostridium*, *Lachnospira*	[16]
	70 patients with coronary artery disease	*Escherichia-Shigella*, *Enterococcus*	*Faecalibacterium*, *Roseburia*, *Subdoligranulum*, *Eubacterium rectale*	[17]
Atrial fibrillation	34 atrial fibrillation patients	*Enterobacter*	*Parabacteroides*, *Lachnoclostridium*, *Streptococcus*, *Alistipes*	[18]

真杆菌属细菌不仅能产生SCFAs, 还能降低胆固醇水平, 调节胆汁酸 (bile acids, BAs) 代谢, 促进肠道和肝脏健康, 从而降低CVD风险[29]。

1.3　HF　HF是指心脏泵血功能降低而无法满足机体需要的一种严重状况, 也是许多CVD发展的终末阶段[30]。CHF是最常见的HF类型。在CHF患者和动物模型中, 肠球菌属*Enterococcus*细菌和埃希氏−志贺氏菌*Escherichia-Shigella*的相对丰度明显升高, 栖粪杆菌属*Faecalibacterium*和瘤胃球菌科*Ruminococcaceae*细菌的相对丰度明显降低, 在AS、高血压和冠心病患者中同样存在上述变化[8,9,12-14,16]。研究表明, 脂多糖 (lipopolysaccharide, LPS) 水平升高是AS发生发展的严重危险因素[31]。而埃希氏−志贺氏菌的增殖伴随着LPS水平升高, 使肠道通透性增加, 可能导致LPS易位[32]。瘤胃球菌科细菌是SCFAs产生菌, 可改善代谢性内毒素血症和肠道菌群失调引起的慢性炎症[33]。大多数肠球菌属细菌是共生菌, 但有部分菌株是条件性致病菌, 如粪肠球菌*Enterococcus faecalis*和屎肠球菌*Enterococcus faecium*, 可引起尿路感染、化脓性腹腔感染、败血症、心内膜炎和腹泻等[34]。栖粪杆菌属细菌仅由普氏栖粪杆菌组成, 是一种丁酸产生菌, 也是肠道健康的生物标志物[35]。丁酸可以减少黏附分子、细胞因子的产生, 抑制氧化应激和炎症, 减轻肿瘤坏死因子α (tumour necrosis factor α, TNF-α) 诱导的单核细胞与内皮细胞的黏附[36]。

1.4　其他心血管疾病　研究发现, 心房颤动患者中肠杆菌属*Enterobacter*细菌的相对丰度显著升高, 另枝菌属*Alistipes*细菌的相对丰度显著降低, 这些变化与AS患者一致[10,18]。肠杆菌属细菌可引起多种临床感染, 包括脑膜炎、败血症、伤口、泌尿道和腹腔内感染等[37]。另枝菌属与CVD直接相关, 其丰度降低伴随着SCFAs水平降低[38]。慢性炎症导致的内皮细胞功能障碍是心血管危险因素[39]。SCFAs可抑制炎症因子, 如LPS、TNF-α、白细胞介素 (interleukin, IL)-6、IL-8的产生, 还能促进抗炎因子IL-10的表达[40]。不同CVD患者肠道菌群变化都存在SCFAs产生菌丰度降低的现象, 这也暗示SCFAs在CVD中的治疗潜力。此外, CVD患者肠道中的厚壁菌门和拟杆菌门细菌的比例 (Firmicutes/Bacteroidetes, F/B) 也发生了变化。厚壁菌门和拟杆菌门细菌可通过发酵膳食纤维产生SCFAs, 从而作用于肠内分泌细胞表达的G蛋白偶联受体 (G protein coupled receptors, GPCRs) 来影响宿主代谢[41]。研究表明, 心房颤动的持续时间与肠道菌群紊乱相关, 持续性心房颤动超过12个月和小于12个月的患者肠

道菌群失调有许多共同特征, 并且菌群失调随着持续时间的延长而加重, 如肠道菌群多样性升高、肠型分布改变、有益菌减少及病原菌富集[42]。这些证据足以说明, 肠道菌群不仅参与CVD的发展, 在疾病早期监控肠道菌群的变化并加以控制也有助于预防和治疗。

2 肠道菌群代谢产物与心血管疾病的关联

肠道菌群可以分解宿主体内未消化的食物, 产生一系列对机体有益或有害的代谢产物, 如氧化三甲胺(trimethylamine-*N*-oxide, TMAO)、BAs、SCFAs、苯乙酰谷氨酰胺 (phenylacetylglutamine, PAGln)、色氨酸和吲哚衍生物等, 它们在CVD的发生、发展、诊断和治疗中起着重要作用[43]。

2.1 胆汁酸 肝脏中的胆固醇能合成初级胆汁酸, 其合成途径主要有两种, 胆固醇7α-羟化酶 (CYP7A1) 催化生成胆酸和鹅去氧胆酸为经典途径, 经胆固醇27-羟化酶 (CYP27A1) 催化生成鹅去氧胆酸为替代途径, 初级胆汁酸进入肠道后被肠道菌群转化为次级胆汁酸。BAs可通过激活不同的BAs受体来影响免疫功能和宿主代谢, 包括法尼醇X受体 (farnesoid X receptor, FXR)、G蛋白偶联受体5 (TGR5)、孕烷X受体 (pregnane X receptor, PXR) 和维生素D受体 (vitamin D receptor, VDR)[44]。激活BAs的核受体FXR能阻断高甘油三酯血症和非高密度脂蛋白胆固醇的升高, 防止AS病变的形成[45]。FXR能改善脂肪组织来源的间充质干细胞 (mesenchymal stromal cells, MSC) 的存活率, 并增强MSC旁分泌血管生成, 从而提高MSC对缺血性心脏损伤的保护作用[46]。TGR5是BAs膜受体, 可调节心肌梗死 (myocardial infarction, MI) 后心脏中CD4 T细胞功能及细胞亚群Th1和Treg的聚集, 对心脏具有保护作用[47]。TGR5还可通过AKT/GSK-3β信号通路, 减轻心肌缺血/再灌注 (ischemia/reperfusion, I/R) 损伤诱导的线粒体功能障碍和细胞凋亡以及炎症[48]。此外, VDR可作为一种内源性心脏保护受体, 在心肌I/R后表达上调, 抑制细胞凋亡和自噬功能障碍介导的细胞死亡[49]。

2.2 SCFAs SCFAs不仅作为肠上皮细胞的营养物质和能量来源, 还可激活GPCRs和抑制组蛋白去乙酰化酶 (histone deacetylase, HDAC), 具有调节代谢、免疫和炎症等作用[50]。研究表明, 西方饮食缺乏膳食纤维的摄入, 导致SCFAs的产生和GPCR43/109A信号传导减少, 易诱发高血压[51]。丙酸可通过嗅觉受体78 (olfactory receptor 78, Olfr78) 和GPCR41降低血压, 在体外诱导血管舒张, 在小鼠体内产生急性降压反应[52]。血管紧张素II (angiotensin II, AngII) 能通过CAV-1/ACE2轴加重心肌I/R损伤, 而丙酸可通过GPCR41抑制AngII水平升高, 从而缓解心肌I/R损伤[53]。丙酸还可增加肠道中IL-10和Treg细胞的水平并抑制胆固醇转运蛋白的表达来调控肠道胆固醇稳态, 从而预防AS[54]。丁酸钠能抑制HDAC5和HDAC6的活性以及COX2/PGE2信号通路的激活, 最终减轻AngII诱导的心肌肥大[55]。丁酸可通过PPARδ/miR-181b信号通路减少内皮细胞中NADPH氧化酶2 (NADPH oxidase 2, NOX2) 的表达和ROS的产生, 从而改善内皮功能和预防AS[56]。丁酸还可通过促进巨噬细胞M2极化来抑制炎症反应和交感神经重构, 从而改善MI后的心脏功能, 预防室性心律失常[57]。此外, 口服丁酸补充剂能减少MI面积, 减轻细胞凋亡、氧化应激和炎症, 通过肠脑神经回路改善心肌I/R损伤[58]。

2.3 TMAO TMAO主要来源于牛肉、鸡蛋或鱼虾中富含的胆碱、肉碱和甜菜碱, 这些物质在肠道中被肠道菌群代谢为三甲胺 (trimethylamine, TMA), 经门静脉吸收进入血液循环后, 被肝脏中的含黄素单加氧酶3 (flavin-containing monooxygenase 3, FMO3) 转化为TMAO[59]。研究表明, 通过膳食补充TMAO会促进与AS相关的多种巨噬细胞清道夫受体上调和泡沫细胞的形成[60]。TMAO血浆水平的增加会导致血浆渗透压升高, 促进水通道蛋白2 (aquaporin-2, AQP-2) 的表达, 从而引起更多的水被重吸收而诱导高血压[61]。TMAO可促进心肌成纤维细胞的增殖、迁移和胶原蛋白的分泌, 通过激活NLRP3炎症小体和氧化应激, 加重小鼠心肌纤维化[62]。TMAO可增加AS斑块内巨噬细胞的迁移和募集, 促进炎症因子的表达, 通过MAPK/JNK信号通路上调氧化低密度脂蛋白诱导CD36的表达和泡沫细胞形成[63]。而通过给药降低TMAO浓度可促进巨噬细胞M2极化和胞葬作用, 减少颈部AS斑块大小并增强斑块的稳定性[64]。TMAO能上调与CVD相关的miR-30c-5p和miR-21-5p的表达, 并影响其共同靶基因PER2的表达, 从而促进炎症和AS的发展[65]。此外, TMAO可通过Beclin 1信号通路阻断自噬流, 从而加剧血管内膜增生[66]。

2.4 其他肠道菌群代谢产物 PAGln是肠道菌群代谢产物之一, 由营养前体代谢物苯丙氨酸产生, 可通过GPCRs, 包括α2A、α2B和β2-肾上腺素能受体介导细胞反应, 促进血小板聚集和血栓形成[67]。PAGln能激活TLR4/AKT/mTOR信号通路, 促进炎症和心肌纤维化, 从而增加HF小鼠室性心律失常的易感性[68]。循环PAGln水平与HF的严重程度指数密切相关, PAGln可促进HF相关的表型, 包括心肌细胞肌节收缩减少和B型利钠肽 (BNP) 基因的表达[69]。支链氨基酸 (branched chain amino acids, BCAAs) 包括亮氨酸、异

亮氨酸和缬氨酸, 是心脏中可高度分解代谢的一组必需氨基酸[70]。BCAAs可通过GCN2/ATF6信号通路加剧脂质过氧化毒性, 使心肌对I/R损伤的易损性增加[71]。BCAAs在MI后的缺血性心脏中过度积累, 通过mTORC1/DUX4/KDM4E轴使MSC早衰和死亡, 从而抑制其对缺血性心脏损伤的保护[72]。色氨酸是具有吲哚结构的氨基酸, 研究发现其吲哚衍生物与不良心血管事件之间存在正相关[73]。硫酸吲哚醇是最具代表性的色氨酸代谢物之一, 其促进炎症和氧化作用与CVD及其并发症的发病机制有关[74]。硫酸吲哚醇可通过ITGβ1/ERK信号通路促进人脐静脉平滑肌细胞的黏附、增殖和迁移, 从而诱导血管功能障碍[75]。此外, 硫酸吲哚醇可通过AHR/NF-κB信号通路激活心脏NLRP3炎症小体, 并上调多种炎症因子, 诱发心脏纤维化和心脏肥大并且损伤左心室功能[76]。

3 中药靶向肠道菌群治疗心血管疾病的策略

中药是我国独特的卫生资源, 其来源天然, 毒副作用小且安全范围广, 具有多组分和多靶点的特点。中药口服后在肠道中被吸收, 其得以发挥治疗作用离不开肠道菌群的贡献。如表2[77-81]所示, 中药可以调节肠道菌群及其代谢产物, 恢复肠道菌群的多样性, 保护肠黏膜屏障, 增强肠道免疫功能, 从而发挥治疗CVD的作用。

3.1 调整肠道菌群的组成 中药可通过影响肠道菌群的组成, 促进有益菌的生长, 发挥其对CVD的治疗作用。如绞股蓝皂苷XLIX可显著增加F/B比值, 通过降低拟梭菌属*Clostridioides*和脱硫弧菌科*Desulfovibrionaceae*细菌的相对丰度来抑制TMA产生, 增加真杆菌属、罗斯氏菌属、双歧杆菌属、乳酸杆菌属和普雷沃氏菌属细菌的相对丰度来促进丁酸产生, 减轻$APOE^{-/-}$小鼠炎症反应并抑制氧化应激[77]。清心解郁颗粒能富集苏黎世杆菌属*Turicibacter*和罗斯氏菌属细菌, 调节宿主的脂质和类固醇代谢, 增加丁酸的产生, 从而改善$APOE^{-/-}$小鼠的血脂异常和炎症反应[78]。人参皂苷Rc可恢复肠道菌群组成和宿主代谢, 降低总胆固醇和甘油三酯等血脂水平, 抑制炎症因子水平(TNF-α、IL-6和IL-1β), 最终减轻$APOE^{-/-}$小鼠主动脉病变、血脂紊乱和全身炎症[9]。姜黄素可显著增加*Unspecific_S24_7*和艾克曼菌属*Akkermansia*细菌的相对丰度, 从而恢复脂质代谢和TMAO合成, 减小AS斑块大小, 减轻巨噬细胞M1极化和炎症反应[82]。

3.2 保护肠黏膜屏障 肠黏膜屏障是抵御病原体侵袭的重要防线, 可保护内环境稳态, 防止有害物质易位进入血液循环[83]。“肠漏”假说认为, 由于肠壁水肿和HF期间肠黏膜屏障功能受损会导致肠道通透性增加, 使细菌内毒素易位, 从而加剧HF的发展[84]。肠上皮细胞间的紧密连接由几种跨膜蛋白和胞浆蛋白组成, 包括occludin、claudins、zonula occludens (ZO)、tricellulin、cingulin、junctional adhesion molecules, 为维持肠黏膜屏障的完整性发挥着关键作用, 若紧密连接被破坏会导致大量抗原分子或微生物通过细胞旁途径, 进一步加重炎症反应[85]。小檗碱可显著增加艾克曼菌属细菌的相对丰度, 并增加occludin和ZO-1的表达及结肠黏液层的厚度, 从而减轻$APOE^{-/-}$小鼠全身炎症和高胆固醇血症, 增加肠道屏障完整性[86]。姜黄素可通过增加ZO-1和claudin-1的表达来改善肠黏膜屏障功能, 从而减少LPS易位, 明显减轻AS的炎症状况[87]。脓毒症是CVD的重要危险因素, 它会引起慢性全身炎症, 将稳定的AS斑块转化为不稳定而破裂, 进而引发脑卒中或AMI[88]。研究显示, 大黄单体可显著增加紧密连接蛋白 (ZO-1、occludin和claudin-5) 的表达, 改善脓毒症大鼠的肠黏膜屏障损伤[89]。大黄素可通过VDR/Nrf2/HO-1信号通路减轻炎症和氧化应激, 保护脓毒症小鼠的肠黏膜屏障[90]。

Table 2 Research on the regulation of gut microbiota by traditional Chinese medicine for cardiovascular diseases. TCM: Traditional Chinese medicine; TMA: Trimethylamine; BA: Bile acid; AS: Atherosclerosis

TCM ingredient/ prescription	Effect on gut microbiota		Effect on metabolites of gut microbiota	Therapeutic effect	Ref.
	Promote	Reduce			
Gypenoside XLIX	*Eubacterium*, *Roseburia*, *Bifidobacterium*, *Lactobacillus*, *Prevotella*	*Clostridioides*, *Desulfovibrionaceae*	Inhibited TMA production and promoted SCFAs production	Reduced dyslipidemia, atherosclerotic plaque, and inflammation	[77]
Qing-Xin-Jie-Yu Granule	*Turicibacter*, *Roseburia*	*Alistipes*, *Rikenella*, *Blautia*	Regulation of BA metabolism	Reduced weight, alleviated dyslipidemia, improved AS and inflammation	[78]
Dendrobium officinale polysaccharide	*Lachnospiraceae_NK4A136_group*, *Lactobacillus*, *NK4A214_group*	*Blautia*	Increased the levels of SCFAs	Lowered blood pressure, enhanced intestinal barrier, improved vascular endothelial function	[79]
Lycium barbarum polysaccharide	*Gordonibacter*, *Parabacteroides*, *Anaerostipes*	–	Increased indole derivatives of tryptophan metabolites	Decreased intestinal permeability and reduced myocardial damage	[80]
Polygonatum sibiricum Red. superfine powder	*Streptococcus* species	*Desulfobacter* and *Desulfovibrio* species	Increased the levels of SCFAs	Enhanced intestinal barrier integrity, improved vascular endothelial function, and lowered blood pressure	[81]

3.3　影响肠道免疫功能　肠道免疫系统主要由肠道相关淋巴组织 (gut associated lymphoid tissue, GALT)、分泌型免疫球蛋白 A (secreted immunoglobulin A, SIgA) 和免疫细胞组成[91]。作为人体最大的免疫器官, GALT能特异性识别外来抗原, 促进细胞因子和抗体的产生来协调免疫反应[92]。SIgA可以刺激肠黏液的分泌, 防止细菌黏附在肠黏膜上, 保护肠道免受外来抗原的破坏, 避免激活异常的免疫反应[93]。SIgA对调节肠道菌群组成并维持肠道微生态平衡至关重要。肠道菌群失调会导致全身免疫应答的激活增强, SIgA可减少炎症反应, 调节肠道菌群组成, 保护机体免受不当的免疫反应, 并维持肠道稳态[94]。研究显示, 人参皂苷可通过调节肠道菌群组成改善*APOE*$^{-/-}$小鼠主动脉病变、血脂紊乱和全身炎症[9]。人参皂苷与西洋参多糖协同作用可对GALT发挥免疫调节作用, 并且通过逆转脾脏和外周血淋巴细胞亚群比例, 以及刺激小肠中CD4 T细胞和SIgA的形成来缓解肠道免疫紊乱, 微生物组–代谢组学分析结果显示, 它们可以恢复肠道菌群组成, 并且改变与免疫代谢或肠道屏障保护作用相关的多种粪便代谢物[95,96]。因此, 人参皂苷可能是通过调节肠道菌群组成, 促进SIgA的形成, 从而改善CVD患者的肠道免疫功能。清心解郁颗粒能通过调节肠道菌群稳态及BAs代谢途径, 改善*APOE*$^{-/-}$小鼠的血脂异常和炎症反应[78]。研究显示, BAs可以通过不同的受体和细胞信号通路来调控结肠T淋巴细胞分化, 调节TH17和Treg细胞群的比例来维持肠道免疫系统[97]。鉴于此, 清心解郁颗粒可能是通过调节肠道菌群和BAs代谢来发挥肠道免疫调节作用, 最终达到缓解AS的目的。

3.4　调控肠道菌群代谢产物　目前, 中药多糖与肠道菌群的相互作用得到广泛研究。多糖可通过调节肠道菌群影响机体代谢、免疫和炎症反应[98]。人类基因组编码的酶难以将多糖分解代谢, 但结肠中的细菌能将其降解为可以被人体吸收和利用的SCFAs[99]。如铁皮石斛多糖可通过激活肠道SCFAs-GPCR43/41通路, 调节脂质代谢、增强肠道屏障、改善血管功能[79]。枸杞多糖可降低TMAO的血浆浓度, 增加参与烟酸、烟酰胺和嘌呤代谢途径的代谢物以及色氨酸吲哚衍生物的水平, 降低肠道通透性和炎症因子水平, 从而改善高脂饮食喂养小鼠的左心室功能[80]。黄精超细粉中的多糖成分可增加结肠中的SCFAs, 改善肠道屏障功能, 显著减少LPS易位, 并抑制TLR4/MyD88信号通路的激活, 减少血管内皮损伤[81]。高脂血症为常见的代谢综合征, 其特征是血脂水平升高, 是CVD的首要病因和病理基础[100]。佛手柑多糖和老香黄多糖通过恢复肠道菌群变化, 增加肠道中SCFAs的产生并改善代谢异常, 从而促进高脂血症患者的肠道健康[101]。除多糖外, 老鹳草素可通过重塑肠道菌群抑制TMAO的合成, 减轻*APOE*$^{-/-}$小鼠的病变面积[102]。小檗碱可通过抑制肠道中胆碱三甲胺裂解酶和黄素单加氧酶的活性, 显著降低TMAO的合成, 达到治疗AS的目的[103]。

4　总结与展望

随着测序技术和质谱技术的发展, 肠道微生物组的研究取得了巨大的进步。越来越多的研究表明, 肠道微生物组和宿主健康、药物 (包括中药) 干预密切相关。尽管目前对宿主–微生物群相互作用的理解越来越深入, 仍然十分缺乏对大多数肠道菌群代谢产物功能的理解。如何更加全面地理解肠道微生物组–宿主代谢的相互作用机制仍是目前重要且必要的课题, 这将有助于了解疾病的病理生理机制和药物干预机制, 为开发新的治疗方法和药物奠定基础。

微生物群作为机体生态系统的可塑性部分, 微生物不仅影响其特定肠道部位的化学性质, 还影响远处环境的化学成分 (如脑、心脏、肝脏系统等), 肠道微生物群被认为是有助于调节宿主健康的关键因素之一[104]。微生物组研究也越来越强调化学环境是如何塑造微生物群落以及对微生物衍生代谢物在机体生态系统功能更深层次的理解[105]。基于质谱的代谢组学可检测和鉴定微生物组产生的小分子, 是了解这些微生物衍生代谢物的功能作用的关键技术之一。代谢组学处于所有组学技术的最下游, 最接近生物表型, 主要通过考察生物系统在某一特定时期内受到刺激或扰动前后所有小分子代谢物 (一般分子量小于1 500 Da) 的组成及含量变化[106]。微生物组和代谢组的联合分析极大地促进了对疾病病理机制和中药疗效机制的理解, 却依旧缺乏对大多数中药调控微生物衍生代谢物功能的理解。虽然质谱技术和微生物测序技术的发展促进了对微生物及其代谢产物的了解, 但是数据分析仍具有相当大的挑战性, 为了更深入地了解微生物组如何影响宿主健康和药物干预的机制, 必须建立大量微生物衍生代谢物及其功能清单, 并且包括了解它们相互联系以及微生物如何处理不同代谢物 (内源性代谢物、天然产物和药物) 的数据库[107-109]。因此, 必须提高在功能层面上对微生物组生物化学反应的理解, 如微生物与其他微生物和宿主细胞类型相互作用的化学性质, 化学暴露对微生物组的影响等。

肠道菌群来源的代谢产物与许多疾病有着密切关系, 对宿主的生理机能产生根本性影响。含羧基和羰基类代谢物是一类重要的肠道菌群代谢产物, 参与多种生化途径, 它们的失调与多种病理状态有关[110]。然

而, 这类代谢物较差的电离特性使其极难分析, 如何提高对这类代谢物的检测对于了解机体生理病理机制至关重要[111]。多种化学同位素标记和化学衍生化的方法被运用到这类代谢物的分析中, 极大地促进了对这类代谢物的检测[112-114]。然而, 这些靶向代谢组学方法仍存在一定的局限性, 就是它们只能对检测目录中的已知代谢物进行靶向检测, 不能完全覆盖因疾病或药物干预引起的肠道菌群代谢产物的变化, 并且无法发现未知代谢产物的水平变化。最新的研究开发了一种新的化学生物学工具, 利用化学选择性修饰的策略来克服羰基分析的局限性, 实验中设计了两种同位素探针, 它们能够对不同生物样本中超过200种代谢物进行飞克级半定量分析和埃摩尔级的定性分析[115]。和前述靶向代谢组学相比, 这种加入化学同位素探针的方式虽然没有明显提升检测代谢物的数量, 却能发现更多未知的肠道菌群代谢产物, 促进对肠道微生物组的了解。针对肠道菌群代谢产物的分析, 后续可以考虑将化学生物学工具和化学衍生物试剂相结合的方式, 这将极大提高检测这类代谢物的灵敏度。此外, 引入拟靶向代谢组学数据采集方式[116], 将进一步提高代谢物定量的准确度。

1970年, 研究报道了一种海洋费氏弧菌 *Vibrio fischeri* 的菌群密度与发光现象呈正相关, 并提出该发光现象受细菌本身的群体感应 (quorum sensing, QS) 调节系统所控制[117]。QS是细菌响应周围环境中同种细菌密度释放和感应信号分子并调控相关基因表达的细胞间通讯过程; QS信号分子也被称为自体诱导分子, 在细胞内产生然后被动或主动地分布在周围环境中, 使细菌能够相互交流, 传递同种细菌密度信息并安排群体活动[118]。当前, 细菌QS的调控机制已得到广泛研究, 通过QS靶向治疗, 如QS信号分子的酶降解 (群体淬灭) 或使用群体感应抑制剂, 可以调节相应的微生物菌落组成, 而不会产生与传统抗菌方法相关的负面影响[119]。生物膜是细菌抗生素耐药的群体行为, 研究显示, QS参与调节细菌生物膜的形成, 而各种病原体可以通过QS以生物膜的形式存在[120]。中药及其活性成分可通过调控细菌QS系统来抑制细菌生物膜的形成并降低毒力因子的产生[121]。如穿心莲内酯能显著降低AGR基因的表达和AGR启动子P2的活性, 对QS系统产生抑制作用, 还能明显降低单核细胞增生李斯特菌 *Listeria monocytogenes* 生物膜的形成和毒力因子的产生[122]。小檗碱能下调AGR基因的表达, 通过抑制细胞间黏附多糖的产生来破坏耐甲氧西林金葡菌 (MRSA) 的QS系统, 从而抑制MRSA生物膜的形成[123]。生物膜引起的慢性感染对临床治疗构成了巨大威胁, 而现代医学治疗长期使用化学药物往往存在毒副作用大和产生耐药性等问题。尽管许多中药表现出对肠道菌群的调节作用, 但是否通过QS信号分子传导, 仍然未知。

近年来, 随着组学数据的结构复杂化和大数据分析需求的不断增加, 人工智能 (artificial intelligence, AI) 在组学研究中得到了广泛的应用[124]。AI是指创建一个智能系统, 能够执行通常需要人类智慧的任务, 基于学习得出针对特定目标的解决方案[125]。机器学习 (machine learning, ML) 是AI的分支学科, 是实现AI的一种方法, 能凭借丰富的算法和学习特征分析和解释复杂且量大的数据, 根据数据类型和训练策略, 主要分为有监督学习和无监督学习[126]。在代谢组学的工作流程中, 经常面临信号处理与数据分析的问题, 由于环境和仪器等因素所引起的不良信号波动, 会严重影响后续的分析结果。研究报道了一种基于ML的代谢组学信号处理的新方法, 通过大规模扫描数千个信号处理流程, 快速优化出针对现有原始数据的处理流程, 这一方法实现了时间过程和多类代谢组学的数据处理, 对于药物代谢与疾病发生发展的病理学机制研究具有重要的价值[127]。此外, 在人类肠道菌群研究产生的大数据中, ML可用于表型预测、发现生物标志物、无创性评估疾病风险或设计肠道菌群靶向治疗, 还可以根据肠道菌群对患者进行分层及疾病亚型分类, 有助于个体化的治疗[128]。ML还能辅助构建人类肠道菌群的QS通信网络, 从而有助于构建人类肠道菌群的关键知识图谱, 支持未来的应用[129], 促进对疾病生理病理机制和中药干预机制的了解。ML的发展和应用推进了研究人员在生物学和医学上的观察发现, 促进了精准医疗的发展, 有助于识别个体差异、提高治疗效率、减少不良反应、降低医疗成本。

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References

[1] Ma LY, Wang ZW, Fan J, et al. An essential introduction to the annual report on cardiovascular health and diseases in China (2021) [J]. Chin Gen Pract (中国全科医学), 2022, 25: 3331-3346.

[2] Trillenberg P, Katalinic A, Thern J, et al. The risk of worsening of myasthenia by cardiovascular medication as reflected by reporting frequency [J]. Eur J Neurol, 2021, 28: 2965-2970.

[3] Hu J, Wang XH, Gao S, et al. Progress in research on anti-tumor

mechanism of NK cell and its related immunotherapy [J]. Chin Pharmacol Bull (中国药理学通报), 2019, 35: 1496-1500.

[4] Guo SS, Chen HY, Li Y, et al. Research progress on traditional Chinese medicine regulating intestinal flora to prevent and treat cardiovascular disease [J]. Chin Arch Tradit Chin Med (中华中医药学刊), 2020, 38: 132-135.

[5] Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2016 update: a report from the American Heart Association [J]. Circulation, 2016, 133: e38-e360.

[6] Zhao J, Zhang Q, Cheng W, et al. Heart-gut-microbiota communication determines the severity of cardiac injury after myocardial ischemia/reperfusion [J]. Cardiovasc Res, 2023, 119: 1390-1402.

[7] Lin Z, Zu XP, Xie HS, et al. Research progress in mechanism of intestinal microorganisms in human diseases [J]. Acta Pharm Sin (药学学报), 2016, 51: 843-852.

[8] Jie Z, Xia H, Zhong SL, et al. The gut microbiome in atherosclerotic cardiovascular disease [J]. Nat Commun, 2017, 8: 845.

[9] Xie B, Zu X, Wang Z, et al. Ginsenoside Rc ameliorated atherosclerosis *via* regulating gut microbiota and fecal metabolites [J]. Front Pharmacol, 2022, 13: 990476.

[10] Qi Y, Liu W, Yan X, et al. Tongxinluo may alleviate inflammation and improve the stability of atherosclerotic plaques by changing the intestinal flora [J]. Front Pharmacol, 2022, 13: 805266.

[11] Han Y, Gong Z, Sun G, et al. Dysbiosis of gut microbiota in patients with acute myocardial infarction [J]. Front Microbiol, 2021, 12: 680101.

[12] Cui X, Ye L, Li J, et al. Metagenomic and metabolomic analyses unveil dysbiosis of gut microbiota in chronic heart failure patients [J]. Sci Rep, 2018, 8: 635.

[13] Wu X, Zhang N, Kan J, et al. Polyphenols from *Arctium lappa* L ameliorate doxorubicin-induced heart failure and improve gut microbiota composition in mice [J]. J Food Biochem, 2022, 46: e13731.

[14] Sun W, Du D, Fu T, et al. Alterations of the gut microbiota in patients with severe chronic heart failure [J]. Front Microbiol, 2021, 12: 813289.

[15] Qin Y, Zhao J, Wang Y, et al. Specific alterations of gut microbiota in Chinese patients with hypertension: a systematic review and meta-analysis [J]. Kidney Blood Press Res, 2022, 47: 433-447.

[16] Zhong J, Wu D, Zeng Y, et al. The microbial and metabolic signatures of patients with stable coronary artery disease [J]. Microbiol Spectr, 2022, 10: e246722.

[17] Zhu Q, Gao R, Zhang Y, et al. Dysbiosis signatures of gut microbiota in coronary artery disease [J]. Physiol Genomics, 2018, 50: 893-903.

[18] Tabata T, Yamashita T, Hosomi K, et al. Gut microbial composition in patients with atrial fibrillation: effects of diet and drugs [J]. Heart Vessels, 2021, 36: 105-114.

[19] Du LY, Li QY, Chen WZ, et al. Progress in research on the relationship between pro-inflammatory gut microbiota and atherosclerosis [J]. Food Sci (食品科学), 2022, 43: 325-332.

[20] Pitout JD, Nordmann P, Poirel L. Carbapenemase-producing *Klebsiella pneumoniae*, a key pathogen set for global nosocomial dominance [J]. Antimicrob Agents Chemother, 2015, 59: 5873-5884.

[21] Zhao X, Zhong X, Liu X, et al. Therapeutic and improving function of *Lactobacilli* in the prevention and treatment of cardiovascular-related diseases: a novel perspective from gut microbiota [J]. Front Nutr, 2021, 8: 693412.

[22] Tamanai-Shacoori Z, Smida I, Bousarghin L, et al. *Roseburia* spp.: a marker of health? [J]. Future Microbiol, 2017, 12: 157-170.

[23] Precup G, Vodnar DC. Gut *Prevotella* as a possible biomarker of diet and its eubiotic *versus* dysbiotic roles: a comprehensive literature review [J]. Br J Nutr, 2019, 122: 131-140.

[24] Arzamasov AA, van Sinderen D, Rodionov DA. Comparative genomics reveals the regulatory complexity of bifidobacterial arabinose and arabino-oligosaccharide utilization [J]. Front Microbiol, 2018, 9: 776.

[25] Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction [J]. Lancet, 2017, 389: 197-210.

[26] Shetty SA, Marathe NP, Lanjekar V, et al. Comparative genome analysis of *Megasphaera* sp. reveals niche specialization and its potential role in the human gut [J]. PLoS One, 2013, 8: e79353.

[27] Nie Y, Xie XQ, Zhou L, et al. *Desulfovibrio fairfieldensis*-derived outer membrane vesicles damage epithelial barrier and induce inflammation and pyroptosis in macrophages [J]. Cells, 2022, 12: 89.

[28] Telle-Hansen VH, Gaundal L, Bastani N, et al. Replacing saturated fatty acids with polyunsaturated fatty acids increases the abundance of Lachnospiraceae and is associated with reduced total cholesterol levels-a randomized controlled trial in healthy individuals [J]. Lipids Health Dis, 2022, 21: 92.

[29] Mukherjee A, Lordan C, Ross RP, et al. Gut microbes from the phylogenetically diverse genus *Eubacterium* and their various contributions to gut health [J]. Gut Microbes, 2020, 12: 1802866.

[30] Ponikowski P, Anker SD, Alhabib KF, et al. Heart failure: preventing disease and death worldwide [J]. ESC Heart Fail, 2014, 1: 4-25.

[31] Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions [J]. J Am Soc Nephrol, 2014, 25: 657-670.

[32] Flannigan KL, Taylor MR, Pereira SK, et al. An intact microbiota is required for the gastrointestinal toxicity of the immunosuppressant mycophenolate mofetil [J]. J Heart Lung Transplant, 2018, 37: 1047-1059.

[33] Kang C, Wang B, Kaliannan K, et al. Gut microbiota mediates the protective effects of dietary capsaicin against chronic low-grade inflammation and associated obesity induced by high-fat

diet [J]. mBio, 2017, 8: e00470-17.

[34] Byappanahalli MN, Nevers MB, Korajkic A, et al. Enterococci in the environment [J]. Microbiol Mol Biol Rev, 2012, 76: 685-706.

[35] Lopez-Siles M, Duncan SH, Garcia-Gil LJ, et al. *Faecalibacterium prausnitzii*: from microbiology to diagnostics and prognostics [J]. ISME J, 2017, 11: 841-852.

[36] Wang Y, Xu Y, Yang M, et al. Butyrate mitigates TNF-alpha-induced attachment of monocytes to endothelial cells [J]. J Bioenerg Biomembr, 2020, 52: 247-256.

[37] Davin-Regli A, Lavigne JP, Pages JM. *Enterobacter* spp.: update on taxonomy, clinical aspects, and emerging antimicrobial resistance [J]. Clin Microbiol Rev, 2019, 32: e00002-19.

[38] Parker BJ, Wearsch PA, Veloo A, et al. The genus *Alistipes*: gut bacteria with emerging implications to inflammation, cancer, and mental health [J]. Front Immunol, 2020, 11: 906.

[39] Castellon X, Bogdanova V. Chronic inflammatory diseases and endothelial dysfunction [J]. Aging Dis, 2016, 7: 81-89.

[40] Nakkarach A, Foo HL, Song AA, et al. Anti-cancer and anti-inflammatory effects elicited by short chain fatty acids produced by *Escherichia coli* isolated from healthy human gut microbiota [J]. Microb Cell Fact, 2021, 20: 36.

[41] Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease [J]. Nat Rev Microbiol, 2021, 19: 55-71.

[42] Zuo K, Li J, Wang P, et al. Duration of persistent atrial fibrillation is associated with alterations in human gut microbiota and metabolic phenotypes [J]. mSystems, 2019, 4: e00422-19.

[43] Xiong SJ, Yin SZ, Deng WS, et al. Progress of research on the relationship between intestinal flora-related metabolites and cardiovascular diseases [J]. Chin J Prac Intern Med (中国实用内科杂志), 2022, 42: 168-172.

[44] Guan B, Tong J, Hao H, et al. Bile acid coordinates microbiota homeostasis and systemic immunometabolism in cardiometabolic diseases [J]. Acta Pharm Sin B, 2022, 12: 2129-2149.

[45] Hartman HB, Gardell SJ, Petucci CJ, et al. Activation of farnesoid X receptor prevents atherosclerotic lesion formation in *LDLR*$^{-/-}$ and *APOE*$^{-/-}$ mice [J]. J Lipid Res, 2009, 50: 1090-1100.

[46] Xia Y, Xu X, Guo Y, et al. Mesenchymal stromal cells overexpressing farnesoid X receptor exert cardioprotective effects against acute ischemic heart injury by binding endogenous bile acids [J]. Adv Sci, 2022, 9: e2200431.

[47] Wang J, Xu T, Xu M. Roles and mechanisms of TGR5 in the modulation of CD4$^+$ T cell functions in myocardial infarction [J]. J Cardiovasc Transl Res, 2022, 15: 350-359.

[48] Li J, Cheng R, Wan H. Overexpression of TGR5 alleviates myocardial ischemia/reperfusion injury *via* AKT/GSK-3beta mediated inflammation and mitochondrial pathway [J]. Biosci Rep, 2020, 40: BSR20193482.

[49] Yao T, Ying X, Zhao Y, et al. Vitamin D receptor activation protects against myocardial reperfusion injury through inhibition of apoptosis and modulation of autophagy [J]. Antioxid Redox Signal, 2015, 22: 633-650.

[50] Rekha K, Venkidasamy B, Samynathan R, et al. Short-chain fatty acid: an updated review on signaling, metabolism, and therapeutic effects [J]. Crit Rev Food Sci Nutr, 2022, 26: 1-29.

[51] Kaye DM, Shihata WA, Jama HA, et al. Deficiency of prebiotic fiber and insufficient signaling through gut metabolite-sensing receptors leads to cardiovascular disease [J]. Circulation, 2020, 141: 1393-1403.

[52] Pluznick JL, Protzko RJ, Gevorgyan H, et al. Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation [J]. Proc Nat Acad Sci U S A, 2013, 110: 4410-4415.

[53] Deng F, Zhang LQ, Wu H, et al. Propionate alleviates myocardial ischemia-reperfusion injury aggravated by angiotensin II dependent on caveolin-1/ACE2 axis through GPR41 [J]. Int J Biol Sci, 2022, 18: 858-872.

[54] Haghikia A, Zimmermann F, Schumann P, et al. Propionate attenuates atherosclerosis by immune-dependent regulation of intestinal cholesterol metabolism [J]. Eur Heart J, 2022, 43: 518-533.

[55] Zhang L, Deng M, Lu A, et al. Sodium butyrate attenuates angiotensin II-induced cardiac hypertrophy by inhibiting COX2/PGE2 pathway *via* a HDAC5/HDAC6-dependent mechanism [J]. J Cell Mol Med, 2019, 23: 8139-8150.

[56] Tian Q, Leung FP, Chen FM, et al. Butyrate protects endothelial function through PPARdelta/miR-181b signaling [J]. Pharmacol Res, 2021, 169: 105681.

[57] Jiang X, Huang X, Tong Y, et al. Butyrate improves cardiac function and sympathetic neural remodeling following myocardial infarction in rats [J]. Can J Physiol Pharmacol, 2020, 98: 391-399.

[58] Yu Z, Han J, Chen H, et al. Oral supplementation with butyrate improves myocardial ischemia/reperfusion injury *via* a gut-brain neural circuit [J]. Front Cardiovasc Med, 2021, 8: 718674.

[59] Chan MM, Yang X, Wang H, et al. The microbial metabolite trimethylamine *N*-oxide links vascular dysfunctions and the autoimmune disease rheumatoid arthritis [J]. Nutrients, 2019, 11: 1821.

[60] Wang Z, Klipfell E, Bennett BJ, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease [J]. Nature, 2011, 472: 57-63.

[61] Liu M, Han Q, Yang J. Trimethylamine-*N*-oxide (TMAO) increased aquaporin-2 expression in spontaneously hypertensive rats [J]. Clin Exp Hypertens, 2019, 41: 312-322.

[62] Li X, Geng J, Zhao J, et al. Trimethylamine *N*-oxide exacerbates cardiac fibrosis *via* activating the NLRP3 inflammasome [J]. Front Physiol, 2019, 10: 866.

[63] Geng J, Yang C, Wang B, et al. Trimethylamine *N*-oxide promotes atherosclerosis *via* CD36-dependent MAPK/JNK

pathway [J]. Biomed Pharmacother, 2018, 97: 941-947.

[64] Shi W, Huang Y, Yang Z, et al. Reduction of TMAO level enhances the stability of carotid atherosclerotic plaque through promoting macrophage M2 polarization and efferocytosis [J]. Biosci Rep, 2021, 41: BSR20204250.

[65] Diez-Ricote L, Ruiz-Valderrey P, Mico V, et al. Trimethylamine *N*-oxide (TMAO) modulates the expression of cardiovascular disease-related microRNAs and their targets [J]. Int J Mol Sci, 2021, 22: 11145.

[66] Hong Q, Que D, Zhong C, et al. Trimethylamine-*N*-oxide (TMAO) promotes balloon injury-induced neointimal hyperplasia *via* upregulating Beclin1 and impairing autophagic flux [J]. Biomed Pharmacother, 2022, 155: 113639.

[67] Nemet I, Saha PP, Gupta N, et al. A cardiovascular disease-linked gut microbial metabolite acts *via* adrenergic receptors [J]. Cell, 2020, 180: 862-877.

[68] Fu H, Kong B, Zhu J, et al. Phenylacetylglutamine increases the susceptibility of ventricular arrhythmias in heart failure mice by exacerbated activation of the TLR4/AKT/mTOR signaling pathway [J]. Int Immunopharmacol, 2023, 116: 109795.

[69] Romano KA, Nemet I, Prasad SP, et al. Gut microbiota-generated phenylacetylglutamine and heart failure [J]. Circ Heart Fail, 2023, 16: e9972.

[70] Neinast M, Murashige D, Arany Z. Branched chain amino acids [J]. Annu Rev Physiol, 2019, 81: 139-164.

[71] Li Y, Xiong Z, Yan W, et al. Branched chain amino acids exacerbate myocardial ischemia/reperfusion vulnerability *via* enhancing GCN2/ATF6/ PPAR-α pathway-dependent fatty acid oxidation [J]. Theranostics, 2020, 10: 5623-5640.

[72] Zhang F, Hu G, Chen X, et al. Excessive branched-chain amino acid accumulation restricts mesenchymal stem cell-based therapy efficacy in myocardial infarction [J]. Signal Transduct Target Ther, 2022, 7: 171.

[73] Sanchez-Gimenez R, Ahmed-Khodja W, Molina Y, et al. Gut microbiota-derived metabolites and cardiovascular disease risk: a systematic review of prospective cohort studies [J]. Nutrients, 2022, 14: 2654.

[74] Gao H, Liu S. Role of uremic toxin indoxyl sulfate in the progression of cardiovascular disease [J]. Life Sci, 2017, 185: 23-29.

[75] Yu H, Zhou C, Hu D, et al. Uremic toxin indoxyl sulfate induces dysfunction of vascular smooth muscle cells *via* integrin-β1/ ERK signaling pathway [J]. Clin Exp Nephrol, 2022, 26: 640-648.

[76] Yamaguchi K, Yisireyili M, Goto S, et al. Indoxyl sulfate activates NLRP3 inflammasome to induce cardiac contractile dysfunction accompanied by myocardial fibrosis and hypertrophy [J]. Cardiovasc Toxicol, 2022, 22: 365-377.

[77] Gao M, Heng X, Jin J, et al. Gypenoside XLIX ameliorate high-fat diet-induced atherosclerosis *via* regulating intestinal microbiota, alleviating inflammatory response and restraining oxidative stress in *APOE*$^{-/-}$ mice [J]. Pharmaceuticals, 2022, 15: 1056.

[78] Wang A, Guan B, Shao C, et al. Qing-Xin-Jie-Yu granule alleviates atherosclerosis by reshaping gut microbiota and metabolic homeostasis of *APOE*$^{-/-}$ mice [J]. Phytomedicine, 2022, 103: 154220.

[79] Li B, Wang HY, Huang JH, et al. Polysaccharide, the active component of *Dendrobium officinale*, ameliorates metabolic hypertension in rats *via* regulating intestinal flora-SCFAs-vascular axis [J]. Front Pharmacol, 2022, 13: 935714.

[80] Zhang Z, Liu H, Yu B, et al. *Lycium barbarum* polysaccharide attenuates myocardial injury in high-fat diet-fed mice through manipulating the gut microbiome and fecal metabolome [J]. Food Res Int, 2020, 138: 109778.

[81] Su J, Wang Y, Yan M, et al. The beneficial effects of *Polygonatum sibiricum* Red. superfine powder on metabolic hypertensive rats *via* gut-derived LPS/TLR4 pathway inhibition [J]. Phytomedicine, 2022, 106: 154404.

[82] Zhang J, Ou C, Chen M. Curcumin attenuates cadmium-induced atherosclerosis by regulating trimethylamine-*N*-oxide synthesis and macrophage polarization through remodeling the gut microbiota [J]. Ecotoxicol Environ Saf, 2022, 244: 114057.

[83] An J, Liu Y, Wang Y, et al. The role of intestinal mucosal barrier in autoimmune disease: a potential target [J]. Front Immunol, 2022, 13: 871713.

[84] Sandek A, Bauditz J, Swidsinski A, et al. Altered intestinal function in patients with chronic heart failure [J]. J Am Coll Cardiol, 2007, 50: 1561-1569.

[85] Chelakkot C, Ghim J, Ryu SH. Mechanisms regulating intestinal barrier integrity and its pathological implications [J]. Exp Mol Med, 2018, 50: 1-9.

[86] Zhu L, Zhang D, Zhu H, et al. Berberine treatment increases *Akkermansia* in the gut and improves high-fat diet-induced atherosclerosis in *APOE*$^{-/-}$ mice [J]. Atherosclerosis, 2018, 268: 117-126.

[87] Ghosh SS, Bie J, Wang J, et al. Oral supplementation with non-absorbable antibiotics or curcumin attenuates western diet-induced atherosclerosis and glucose intolerance in *LDLR*$^{-/-}$ mice-role of intestinal permeability and macrophage activation [J]. PLoS One, 2014, 9: e108577.

[88] Mankowski RT, Yende S, Angus DC. Long-term impact of sepsis on cardiovascular health [J]. Intensive Care Med, 2019, 45: 78-81.

[89] Wang L, Cui YL, Zhang Z, et al. Rhubarb monomers protect intestinal mucosal barrier in sepsis *via* junction proteins [J]. Chin Med J, 2017, 130: 1218-1225.

[90] Shang L, Liu Y, Li J, et al. Emodin protects sepsis associated damage to the intestinal mucosal barrier through the VDR/ Nrf2 / HO-1 pathway [J]. Front Pharmacol, 2021, 12: 724511.

[91] Sanchez DMF, Romero-Calvo I, Mascaraque C, et al. Intestinal

inflammation and mucosal barrier function [J]. Inflamm Bowel Dis, 2014, 20: 2394-2404.

[92] Shukla A, Chen C, Jellusova J, et al. Self-reactive B cells in the GALT are actively curtailed to prevent gut inflammation [J]. JCI Insight, 2019, 5: e130621.

[93] Donaldson GP, Ladinsky MS, Yu KB, et al. Gut microbiota utilize immunoglobulin A for mucosal colonization [J]. Science, 2018, 360: 795-800.

[94] Pietrzak B, Tomela K, Olejnik-Schmidt A, et al. Secretory IgA in intestinal mucosal secretions as an adaptive barrier against microbial cells [J]. Int J Mol Sci, 2020, 21: 9254.

[95] Biondo PD, Goruk S, Ruth MR, et al. Effect of CVT-E002 (COLD-fX) *versus* a ginsenoside extract on systemic and gut-associated immune function [J]. Int Immunopharmacol, 2008, 8: 1134-1142.

[96] Zhou R, He D, Xie J, et al. The synergistic effects of polysaccharides and ginsenosides from American ginseng (*Panax quinquefolius* L.) ameliorating cyclophosphamide-induced intestinal immune disorders and gut barrier dysfunctions based on microbiome-metabolomics analysis [J]. Front Immunol, 2021, 12: 665901.

[97] Cai J, Sun L, Gonzalez FJ. Gut microbiota-derived bile acids in intestinal immunity, inflammation, and tumorigenesis [J]. Cell Host Microbe, 2022, 30: 289-300.

[98] Shen H, Wu CY, Long F, et al. Meanings of polysaccharides in traditional Chinese medicines decoction from the viewpoint of its gut microbiota regulation effects [J]. Acta Pharm Sin (药学学报), 2022, 57: 3480-3486.

[99] Makki K, Deehan EC, Walter J, et al. The impact of dietary fiber on gut microbiota in host health and disease [J]. Cell Host Microbe, 2018, 23: 705-715.

[100] Nelson RH. Hyperlipidemia as a risk factor for cardiovascular disease [J]. Prim Care, 2013, 40: 195-211.

[101] Zheng Y, Wang Y, Luo D, et al. Effect of bergamot and Laoxianghuang polysaccharides on gut microbiota derived from patients with hyperlipidemia: an integrative analysis of microbiome and metabolome during *in vitro* fermentation [J]. Foods, 2022, 11: 2039.

[102] Lin K, Wang X, Li J, et al. Anti-atherosclerotic effects of geraniin through the gut microbiota-dependent trimethylamine *N*-oxide (TMAO) pathway in mice [J]. Phytomedicine, 2022, 101: 154104.

[103] Ma S, Tong Q, Lin Y, et al. Berberine treats atherosclerosis *via* a vitamine-like effect down-regulating choline-TMA-TMAO production pathway in gut microbiota [J]. Signal Transduct Target Ther, 2022, 7: 207.

[104] de Vos WM, Tilg H, Van Hul M, et al. Gut microbiome and health: mechanistic insights [J]. Gut, 2022, 71: 1020-1032.

[105] Bauermeister A, Mannochio-Russo H, Costa-Lotufo LV, et al. Mass spectrometry-based metabolomics in microbiome investigations [J]. Nat Rev Microbiol, 2022, 20: 143-160.

[106] Wu G, Zhang W, Li H. Application of metabolomics for unveiling the therapeutic role of traditional Chinese medicine in metabolic diseases [J]. J Ethnopharmacol, 2019, 242: 112057.

[107] Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, et al. Mapping human microbiome drug metabolism by gut bacteria and their genes [J]. Nature, 2019, 570: 462-467.

[108] Vich VA, Collij V, Sanna S, et al. Impact of commonly used drugs on the composition and metabolic function of the gut microbiota [J]. Nat Commun, 2020, 11: 362.

[109] Mullard A. Understanding how microbiome bugs metabolize drugs [J]. Nat Rev Drug Discov, 2019, 18: 488.

[110] Singh M, Kapoor A, Bhatnagar A. Oxidative and reductive metabolism of lipid-peroxidation derived carbonyls [J]. Chem Biol Interact, 2015, 234: 261-273.

[111] Gil A, Siegel D, Permentier H, et al. Stability of energy metabolites-an often overlooked issue in metabolomics studies: a review [J]. Electrophoresis, 2015, 36: 2156-2169.

[112] Zhao S, Li L. Dansylhydrazine isotope labeling LC-MS for comprehensive carboxylic acid submetabolome profiling [J]. Anal Chem, 2018, 90: 13514-13522.

[113] Meng X, Pang H, Sun F, et al. Simultaneous 3-nitrophenylhydrazine derivatization strategy of carbonyl, carboxyl and phosphoryl submetabolome for LC-MS/MS-based targeted metabolomics with improved sensitivity and coverage [J]. Anal Chem, 2021, 93: 10075-10083.

[114] Xie G, Wang L, Chen T, et al. A metabolite array technology for precision medicine [J]. Anal Chem, 2021, 93: 5709-5717.

[115] Lin W, Conway LP, Vujasinovic M, et al. Chemoselective and highly sensitive quantification of gut microbiome and human metabolites [J]. Angew Chem Int Ed Engl, 2021, 60: 23232-23240.

[116] Zheng F, Zhao X, Zeng Z, et al. Development of a plasma pseudotargeted metabolomics method based on ultra-high-performance liquid chromatography-mass spectrometry [J]. Nat Protoc, 2020, 15: 2519-2537.

[117] Nealson KH, Platt T, Hastings JW. Cellular control of the synthesis and activity of the bacterial luminescent system [J]. J Bacteriol, 1970, 104: 313-322.

[118] Papenfort K, Bassler BL. Quorum sensing signal-response systems in Gram-negative bacteria [J]. Nat Rev Microbiol, 2016, 14: 576-588.

[119] Fala AK, Alvarez-Ordonez A, Filloux A, et al. Quorum sensing in human gut and food microbiomes: significance and potential for therapeutic targeting [J]. Front Microbiol, 2022, 13: 1002185.

[120] Wang M, Lian Y, Wang Y, et al. The role and mechanism of quorum sensing on environmental antimicrobial resistance [J]. Environ Pollut, 2023, 322: 121238.

[121] Yang M, Gu W, Yang BR, et al. Effect of traditional Chinese medicine in improving human health by regulating bacterial quorum sensing system [J]. China J Chin Mater Med (中国中药

杂志), 2020, 45: 1297-1303.

[122] Yu T, Jiang X, Xu X, et al. Andrographolide inhibits biofilm and virulence in *Listeria monocytogenes* as a quorum-sensing inhibitor [J]. Molecules, 2022, 27: 3234.

[123] Ning Y, Wang X, Chen P, et al. Targeted inhibition of methicillin-resistant *Staphylococcus aureus* biofilm formation by a graphene oxide-loaded aptamer/berberine bifunctional complex [J]. Drug Deliv, 2022, 29: 1675-1683.

[124] Li R, Li L, Xu Y, et al. Machine learning meets omics: applications and perspectives [J]. Brief Bioinform, 2022, 23: bbab460.

[125] Holzinger A, Keiblinger K, Holub P, et al. AI for life: trends in artificial intelligence for biotechnology [J]. N Biotechnol, 2023, 74: 16-24.

[126] Deo RC. Machine learning in medicine [J]. Circulation, 2015, 132: 1920-1930.

[127] Fu J, Zhang Y, Wang Y, et al. Optimization of metabolomic data processing using NOREVA [J]. Nat Protoc, 2022, 17: 129-151.

[128] Li P, Luo H, Ji B, et al. Machine learning for data integration in human gut microbiome [J]. Microb Cell Fact, 2022, 21: 241.

[129] Wu S, Feng J, Liu C, et al. Machine learning aided construction of the quorum sensing communication network for human gut microbiota [J]. Nat Commun, 2022, 13: 3079.